

University of Groningen

Thrombophilia or thrombophobia

Meinardi, Johan Remko

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2001

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Meinardi, J. R. (2001). *Thrombophilia or thrombophobia: clinical implications of recently identified thrombophilic disorders*. s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

CHAPTER 7

INCREASED RISK FOR FETAL LOSS IN CARRIERS OF THE FACTOR V LEIDEN MUTATION

Johan R. Meinardi, Saskia Middeldorp, Pieter J. de Kam,
Maria M.W. Koopman, Elisabeth C.M. van Pampus, Karly Hamulyák,
Martin H. Prins, Harry R. Büller, and Jan van der Meer

Annals of Internal Medicine 1999; 130:736-739

SUMMARY

Background: An increased risk for fetal loss caused by placental thrombosis is probable in carriers of the factor V Leiden mutation but has not been demonstrated consistently in previous studies.

Methods: To assess the risk of fetal loss in carriers of factor V Leiden, we retrospectively collected obstetric data in a cohort of 228 carriers of the factor V Leiden mutation (77 probands, 151 relatives) and 121 noncarrier relatives (controls). All participants had been pregnant at least once. Risks for fetal loss, miscarriage (defined as fetal loss within 20 weeks of gestation), and stillbirth (defined as fetal loss >20 weeks of gestation) in women and in pregnancies were estimated and compared in carriers and noncarriers. Adjusted odds ratios were calculated by using multiple regression analysis. A random-effects model was used for comparisons of pregnancies.

Results: Fetal loss occurred in 31.6% of carriers and 22.3% of noncarriers, miscarriage in 29.4% of carriers and 17.4% of noncarriers, and stillbirth occurred in 5.7% of carriers and 5.0% of noncarriers. Fetal loss recurred in 10.1% of carriers and 4.1% of noncarriers (odds ratio 2.60, [95% CI, 0.96 to 7.03]). Adjusted odds ratios were 2.12 (CI, 1.35 to 3.33) for fetal loss, 2.08 (CI, 1.33 to 3.25) for miscarriage, and 1.60 (CI, 0.58 to 4.43) for stillbirth, when pregnancies in carriers and noncarriers were compared. Homozygous carriers had a greater risk for fetal loss (odds ratio, 2.01 [CI, 0.94 to 4.32]) and stillbirth (odds ratio, 4.85 [CI, 0.82 to 25.58]) than heterozygous carriers.

Conclusions: Carriers of the factor V Leiden mutation have a greater risk for fetal loss (particularly miscarriage) than noncarriers. These data further suggest a greater risk for recurrence of fetal loss in carriers than in noncarriers and a greater risk for fetal loss and stillbirth in homozygous carriers than in heterozygous carriers.

7.1 INTRODUCTION

Hereditary resistance to activated protein C (APC), the most common genetic thrombophilic disorder [1, 2], is mainly caused by a mutation of the factor V gene. This mutation, factor V Leiden, is found in 5% of white persons and is associated with a three- to sevenfold increased risk for venous thromboembolism in heterozygous carriers [3-5]. Fetal loss caused by placental thrombosis may also be related to this disorder, as are hereditary deficiencies of antithrombin, protein C, and protein S [6, 7]. Although several studies reported a greater prevalence of resistance to activated protein C in women with recurrent fetal loss [8-11], other studies did not demonstrate an association [7, 12, 13]. This inconsistency may be caused by differences in selection criteria and small numbers of patients. We performed a retrospective study in a large cohort of women with the factor V Leiden mutation and a group of controls to estimate the risk for fetal loss in carriers of this mutation.

7.2 METHODS

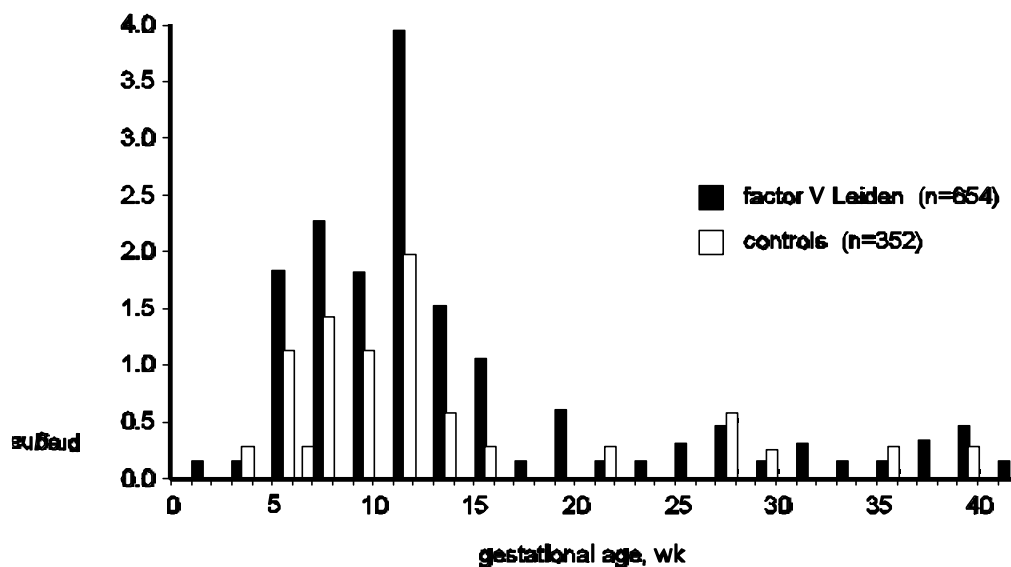
From the patients who were referred to the thrombosis outpatient clinics of the participating hospitals, consecutive patients with proven venous thromboembolism and the factor V Leiden mutation were recruited. These patients were considered *propositi*. Their living first-degree relatives participated in a previous study [5] to assess the absolute risk for venous thromboembolism in carriers of the factor V Leiden mutation. Detailed information about previous thromboembolism, exposure to thrombotic risk factors, and obstetric history was collected by using a standardized medical history form. Relatives were interviewed before polymerase chain reaction was performed to detect heterozygous and homozygous carriers of the factor V Leiden mutation [2]. We analyzed fetal loss by comparing carriers – both *propositi* and relatives – with noncarriers (controls). Written informed consent was obtained from all participants. This study was approved by the institutional review boards of the three participating hospitals.

Women who had been pregnant at least once were eligible for analysis unless they had had only terminated or ectopic pregnancies or had their first pregnancy at study enrollment. Fetal loss that occurred within 20 weeks of gestation was defined as miscarriage, and fetal loss that occurred after more than 20 weeks of gestation was defined as stillbirth, according to the criteria of the World Health Organization [14]. The Wilcoxon two-sample test, the Fisher exact test, and the chi-square test were used when appropriate. Variables that predisposed women to fetal loss were identified by multiple regression analysis. To account for variation in each mother and between mothers, pregnancies were analyzed by a random-effects model for binary data [15]. Variation in first-degree relatives was not considered. The logit link function was used, and the exchangeable correlation structure was assumed in the model. We constructed a population-average random-effects model using the generalized

estimating equation approach [15] and robust estimates of standard error. Evaluated variables were carrier compared with noncarrier, proband compared with relative, age at enrollment, age at time of fetal loss, number of pregnancies per woman, history of venous thromboembolism, anticoagulant treatment during pregnancy, and participating hospital. Only statistically significant ($P < 0.05$) variables at backward selection were included in the final model. Differences between the groups are expressed as adjusted odds ratios with 95% CIs. All P -values are two-tailed. All statistical analyses were performed using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

The funding source did not influence collection, analysis, interpretation, or publication of the data.

Figure 7.1 Distribution of fetal loss related to gestational age in 228 carriers of the factor V Leiden mutation and 121 noncarriers. Percentage of total number of pregnancies in carriers ($n=654$) and noncarriers ($n=352$) is given.



7.3 RESULTS

Of 522 white women (142 probandi, 212 carrier relatives, and 168 noncarrier relatives) who were enrolled in the original study, 173 (65 probandi, 61 carrier relatives, and 47 noncarrier relatives) were excluded from analysis of fetal loss because they had never been pregnant (58 probandi, 59 carrier relatives, and 46 noncarrier relatives); had their first pregnancy at enrollment (2 probandi); or had terminated all of their pregnancies (5 probandi, 2 carrier relatives, and 1 noncarrier relative). We therefore studied 349 women (77 probandi, 151 carrier relatives, and 121 noncarrier relatives). After we excluded 22 terminated and 8

ectopic pregnancies, 228 carriers (of whom 15 were homozygous) had had 654 pregnancies (median, 3 [range, 1 to 12]) and 121 noncarriers had had 352 pregnancies (median, 3 [range, 1 to 10]). Fetal loss per woman ranged from 0 to 6 (median, 0) in carriers and from 0 to 2 (median, 0) in noncarriers. Figure 7.1 shows the distribution of fetal loss related to gestational age in both groups. Median age at enrollment was 49 years (range, 22 to 89 years) for carriers and 50 years (range, 29 to 86 years) for noncarriers.

Of carriers, *propositi* (29.9%) and relatives (32.5%) had a similar risk for fetal loss (odds ratio, 0.89 [CI, 0.49 to 1.61]; $p>0.2$). Fetal loss recurred in 10.1% of carriers and 4.1% of noncarriers (odds ratio, 2.60 [CI, 0.96 to 7.03]; $p=0.06$). Risks for fetal loss are summarized in Table 7.1. Carriers showed a greater risk for fetal loss (31.6% compared with 22.3%) and miscarriage (29.4% compared with 17.4%) than noncarriers. Stillbirth was equally distributed among the groups (5.7% of carriers and 5.0% of noncarriers).

Multiple regression analysis identified the factor V Leiden mutation, the number of pregnancies per woman, and age at enrollment as independent predictors of fetal loss. Age of the woman at time of fetal loss (adjusted odds ratio, 1.00 [CI, 0.97 to 1.04]), type of carrier (*propositus* compared with relative) (adjusted odds ratio, 1.12 [CI, 0.57 to 2.21]), and hospital of recruitment (adjusted odds ratio, 1.10 [CI, 0.57 to 1.61]) were not independent predictors of fetal loss. A history of venous thromboembolism did not influence the occurrence of fetal loss (adjusted odds ratio, 1.21 [CI, 0.70 to 2.09]). Effect of anticoagulant drugs on outcome of pregnancy could not be assessed because these drugs were used during only 2.8% of pregnancies. Exclusion of terminated pregnancies did not influence the results. Adjusted odds ratios, estimated by a random-effects model, were 2.12 (CI, 1.35 to 3.33) for fetal loss, 2.08 (CI, 1.33 to 3.25) for miscarriage, and 1.60 (CI, 0.58 to 4.43) for stillbirth in comparisons of pregnancies in carriers and noncarriers.

A comparison of heterozygous and homozygous carriers suggested an approximately twofold greater risk for fetal loss in homozygous carriers (adjusted odds ratio, 2.01 [CI, 0.94 to 4.32]) (Table 7.1). This was mainly because of an increased risk for stillbirth in homozygous carriers (adjusted odds ratio, 4.85 [CI, 0.82-25.58]).

Table 7.1 Fetal loss in women with the factor V Leiden mutation and their noncarrier relatives

	carriers		non-carriers		odds ratio*	95% CI	P
	n	%	n	%			
women	228		121				
women with fetal loss	72	31.6	27	22.3	2.01	1.07-3.75	0.03
women with miscarriage	67	29.4	21	17.4	2.70	1.39-5.25	0.003
women with stillbirth	13	5.7	6	5.0	1.29	0.45-3.69	> 0.2
pregnancies	654		352				
pregnancies ending in fetal loss**	107	16.4	32	9.1	2.12	1.35-3.33	< 0.001
in heterozygous carriers	96	15.9	32	9.1	2.02	1.34-3.05	< 0.001
in homozygous carriers	9	23.7	32	9.1	4.07	1.66-9.95	< 0.001
in homozygous compared with heterozygous carriers					2.01	0.94-4.32	0.07
pregnancies ending in miscarriage	88	13.5	26	7.4	2.08	1.33-3.25	0.001
in heterozygous carriers	82	13.3	26	7.4	2.03	1.29-3.20	0.002
in homozygous carriers	6	15.8	26	7.4	2.93	1.52-5.77	0.001
in homozygous compared with heterozygous carriers					1.46	0.80-2.66	> 0.2
pregnancies ending in stillbirth	19	2.9	6	1.7	1.60	0.58-4.43	> 0.2
in heterozygous carriers	16	2.6	6	1.7	1.39	0.49-3.96	> 0.2
in homozygous carriers	3	7.9	6	1.7	6.36	1.04-38.93	0.045
in homozygous compared with heterozygous carriers					4.85	0.82-25.58	0.08

* odds ratios, adjusted for age and number of pregnancies, were estimated by random-effects modeling to compare pregnancies

** terminated and ectopic pregnancies excluded

CI = confidence interval

7.4 DISCUSSION

This large retrospective study provides evidence that carriers of the factor V Leiden mutation have a greater risk for fetal loss, particularly miscarriage, than noncarriers. The risk for recurrence of fetal loss also tended to be greater in carriers. Homozygous carriers had the highest frequency of fetal loss and were also more prone to stillbirth than heterozygous carriers. This observation, which was of borderline statistical significance, needs to be confirmed by a study in more homozygous carriers.

Our findings are similar to those of four case-control studies [8-11] that showed a high prevalence of the factor V Leiden mutation in women with recurrent fetal loss, especially fetal loss that occurred in the second or third trimester of pregnancy. Two other studies [12, 13] did not demonstrate such an association in small numbers of cases of recurrent first- or second-trimester fetal loss. A similar retrospective cohort study [7] did not show an increased risk for miscarriage or stillbirth in carriers of the factor V Leiden mutation. In both of these studies, the risk for fetal loss was similar for the control groups (22.3% compared with 23.5%); however, we found a greater risk for fetal loss in carriers than in noncarriers (31.6% compared with 26.9%). This difference may be explained by the possible inclusion in our study of women who had the factor V Leiden mutation and another hereditary thrombophilic disorder. However, it is unlikely that this biased our results, considering the low prevalence of other disorders compared with that of the factor V Leiden mutation. Moreover, other disorders would be equally distributed among carriers and noncarriers, as they were among relatives. Finally, a random-effects model was used to adjust for unexplained sources of heterogeneity in outcomes among mothers. Our estimate of the risk for fetal loss is probably more accurate because we studied a large group of carriers.

Recall bias may have been introduced by the retrospective design of our study – that is, carriers have tended to report more events that occurred during previous pregnancies. This seems unlikely because the medical history was taken in all women, excepted probands, while their factor V Leiden status was unknown. Furthermore, collection of obstetric data primarily addressed pregnancy as a concomitant risk factor for venous thromboembolism. Apart from that, the risk for fetal loss was similar in probands and their relatives who had the factor V Leiden mutation.

In previous studies, fetal loss was classified according to pregnancy trimesters. We preferred the definition of the World Health Organization [14], assuming the viability of a fetus at a body weight of more than 500 gram and a gestation of 20 to 22 weeks. Our results did not change substantially after we redefined miscarriage as fetal loss within 28 weeks of gestation and stillbirth as fetal loss after more than 28 weeks of gestation (data not shown).

It is plausible that fetal loss in carriers of the factor V Leiden mutation is caused by placental thrombosis, as supported by frequently observed placental infarctions in aborted fetuses of carriers [9, 10, 16, 17]. Thrombosis may occur on either side of the maternal-fetal interface. The role of fetoplacental thrombosis has been emphasized by the observation that the carrier frequency of the factor V Leiden mutation in miscarried fetuses was more than

twice that in the general population, and the carrier frequency of the mothers in between [17]. The carrier frequency was 10-fold greater in fetuses with more than 10% placental infarction. These findings suggest that the carrier status of the fetus, rather than that of the mother, is the main determinant of fetal loss. They may also explain why homozygous carriers in our study were more prone to fetal loss than heterozygous carriers. For homozygous carriers, the a priori chance of having a fetus with the factor V Leiden mutation is 100%; for heterozygous carriers, this risk is 50%. Accordingly, we found an approximately twofold greater risk for fetal loss in homozygous carriers than in heterozygous carriers.

The findings of our study and of others could have clinical implications in view of the high prevalence of the factor V Leiden mutation. A prospective follow-up study of carriers with fetal loss may be worthwhile to establish the results of these retrospective studies. If we correctly assume that placental thrombosis is the causal mechanism for fetal loss, carriers with recurrent fetal loss could benefit from anticoagulant treatment. This subgroup, approximately 10% of the carriers in our study, needs to be identified. It may contain homozygous carriers and carriers who have another carrier as a partner. Considering our finding that 80% of the fetal losses occurred within the first 16 weeks of pregnancy, anticoagulant therapy should be started early in pregnancy. Although use of heparin – which does not cross the placenta – is permissible, it may be less effective or ineffective when fetal loss is caused by fetal rather than maternal placental thrombosis. Properly designed clinical trials are needed to assess the supposed benefit and safety of anticoagulant treatment.

7.5 REFERENCES

1. Bertina, R.M., B.P.C. Koeleman, T. Koster, F.R. Rosendaal, R.J. Dirven, H. de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994; 369:64-67.
2. Voorberg, J., J. Roelse, R. Koopman, H. Büller, F. Berends, J.W. ten Cate, et al. Association of idiopathic venous thromboembolism with single point-mutation at Arg⁵⁰⁶ of factor V. *Lancet* 1994; 343:1535-1536.
3. Ridker, P.M., C.H. Hennekens, K. Lindpainter, M.J. Stampfer, P.R. Eisenberg, J.P. Miletich. Mutation in the gene coding for coagulation factor V and the risk for myocardial infarction, stroke and venous thrombosis in apparently healthy men. *New England Journal of Medicine* 1995; 332:912-917.
4. Rosendaal, F.R., T. Koster, J.P. Vandenbroucke, P.H. Reitsma. High risk for thrombosis in patients homozygous for the factor V Leiden mutation (activated protein C resistance). *Blood* 1995; 85:1504-1508.
5. Middeldorp, S., C.M.A. Henkens, M.M.W. Koopman, E.C.M. van Pampus, K. Hamulyák, J. van der Meer, et al. The incidence of venous thromboembolism in family members of patients with the factor V Leiden mutation mutation and venous thrombosis. *Annals of Internal Medicine* 1998; 128:15-20.
6. Sanson, B.J., P.W. Friederich, P. Simioni, S. Zanardi, M.V. Huisman, A. Girolami, et al. The risk for abortion and still birth in antithrombin-, protein C-, and protein S-deficient women. *Thrombosis and Haemostasis* 1996; 75:387-388.
7. Preston, F.E., F.R. Rosendaal, I.D. Walker, E. Briët, E. Berntop, J. Conard, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996; 348:913-916.
8. Rai, R., L. Regan, E. Hadley, M. Dave, H. Cohen. Second-trimester pregnancy loss is associated with activated protein C resistance. *British Journal of Haematology* 1996; 92:489-490.
9. Brenner, B., H. Mandel, N. Lanir, J. Younis, H. Rothbart, G. Ohel, et al. Activated protein C resistance can be associated with recurrent fetal loss. *British Journal of Haematology* 1997; 97:551-554.
10. Grandone, E., M. Margaglione, D. Colaizzo, M. d'Addeda, G. Cappucci, G. Vecchione, et al. The factor V Leiden mutation is associated with repeated and recurrent unexplained fetal losses. *Thrombosis and Haemostasis* 1997; 77:822-824.
11. Ridker, P.M., J.P. Miletich, J.E. Buring, A.A. Ariyo, D.T. Price, J.E. Manson, et al. The factor V Leiden mutation mutation as a risk factor for recurrent pregnancy loss. *Annals of Internal Medicine* 1998;128:1000-1003.
12. Balasch, J., J.C. Reverter, F. Fábregues, D. Tàssies, M. Rafel, M. Creus, et al. First-trimester repeated abortion is not associated with activated protein C resistance. *Human Reproduction* 1997; 12:1094-1097.

13. Dizon-Townson, D.S., S. Kinney, D.W. Branch, K. Ward. The factor V Leiden mutation is not a common cause of recurrent miscarriage. *Journal of Reproduction and Immunology* 1997; 34:217-223.
14. Stirrat, G.M., Recurrent miscarriage I: definition and epidemiology. *Lancet* 1990; 336: 673-675.
15. Diggle, P.J., K.Y. Liang, S. L. Zeger. *Analysis of longitudinal data*. Oxford: Clarendon Press; 1994.
16. Rai, R.S., L. Regan, A. Chitolie, J.G. Donald, H. Cohen. Placental thrombosis and second trimester miscarriage in association with activated protein C resistance. *British Journal of Obstetrics and Gynaecology* 1996; 103:842-844.
17. Dizon-Townson, D.S., L. Meline, L.M. Nelson, M. Varner, K. Ward. Fetal carriers of the factor V Leiden mutation are prone to miscarriage and placental infarction. *American Journal of Obstetrics and Gynecology* 1997; 177:402-405.